Name: Suzana Giffin, AVP
Company/Organization: Merck & Co., Inc.
Address: 2000 Galloping Hill Rd, Kenilworth, NJ 07033
Phone: 908-740-6708
Email: suzana.giffin@merck.com
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NCCN Guidelines Panel: Occult Primary Panel

NCCN Occult Primary Panel: On behalf of Merck & Co., Inc., I respectfully request the NCCN Occult Primary Panel to review the enclosed information for KEYTRUDA® (pembrolizumab), in reference to adenocarcinoma and squamous cell carcinoma.

Specific Changes: We respectfully request the inclusion of pembrolizumab as a treatment option for patients with advanced tumor mutational burden-high (TMB-H) adenocarcinoma and squamous cell carcinoma who have progressed following prior treatment and have no satisfactory alternative treatment to pages OCC-B (2 and 4 of 9) and OCC-B (5 and 7 of 9), respectively, of the NCCN Guidelines for Occult Primary v3.2020.

FDA Clearance: KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Limitations of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with TMB-H central nervous system cancers have not been established.

Rationale: KEYTRUDA is now approved for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors with tissue TMB-H (≥10 mut/Mb), as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options. In a prospectively-planned retrospective analysis of 10 cohorts (A-J) of KEYNOTE-158, a non-randomized, open-label, multicohort study, efficacy and safety of pembrolizumab 200 mg given intravenously every 3 weeks was investigated in 102 previously treated patients with unresectable or metastatic solid tumors with TMB-H, defined as a TMB of ≥10 mut/Mb. The major efficacy outcome measures were objective response rate (ORR) and duration of response (DoR) in the patients who have received at least one dose of KEYTRUDA as assessed by Blinded Independent Central Review according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. The statistical analysis plan pre-specified ≥10 mut/Mb using the FoundationOne®CDx assay as a cutpoint to assess TMB. With a median follow-up time of 11.1 months, ORR was 29% (95% Confidence Interval [CI], 21% to 39%, [n=30/102]) with a complete response rate of 4%. Median DoR was not reached (range, 2.2+ to 34.8+ months). 57% of the patients had a response duration of 12 months or more; 50% of the patients had a response duration of 24 months or more. Safety of KEYTRUDA was investigated in 105 patients with TMB-H cancer in this study. With a median duration of exposure to KEYTRUDA of 4.9 (range: 0.03 to 35.2) months, similar adverse reactions occurred in patients with TMB-H cancer compared to those with other solid tumors who received KEYTRUDA as a single agent. Most common adverse reactions

(reported in ≥20% of patients) with KEYTRUDA as a single agent were: fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain. The above results supported this recent indication for KEYTRUDA.

The following resources are submitted to assist the committee with their review.

1. KEYTRUDA (pembrolizumab) prescribing information. Merck & Co., Inc.
2. Marabelle A, Fakih M, Lopez J, Shah M, Shapira-Frommer R, Nakagawa K, et al. Association of Tumor Mutational Burden with Outcomes in Patients with Select Advanced Solid Tumors Treated with Pembrolizumab in KEYNOTE-158. Annals of Oncology (2019) 30 (suppl_5): v475-v532. 10.1093/annonc/mdz253. Presented at ESMO 2019. September 30, 2019. Barcelona, Spain.

Thank you for considering this request. Below is my contact information should you need to contact me for additional information.

Sincerely,



Suzana Giffin, AVP
Global Medical Affairs
Merck & Co., Inc.
2000 Galloping Hill Rd
Kenilworth, NJ 07033
908-740-6708
suzana.giffin@merck.com